AIMOVIG® (ERENUMAB)

1. NAME OF THE MEDICINAL PRODUCT

[USAN/INN]: erenumab

Trade Name: AIMOVIG®

1.1 Therapeutic/Pharmacological Class

1.1.1 Pharmaceutical Group

Anti-Calcitonin gene-related peptide receptor (anti-CGRPR) monoclonal antibody

1.1.2 ATC Code

N02CD01

1.1.3 Structural Formula Description

- AIMOVIG is a human immunoglobulin G2 (IgG2) monoclonal antibody that has high affinity binding to the CGRP receptor.
- AIMOVIG is composed of two heavy chains, each containing 456 amino acids and two light chains of the lambda subclass, each containing 216 amino acids.
- AIMOVIG has an approximate molecular weight (MW) of 150 kDa.
- AIMOVIG is produced using recombinant DNA technology in Chinese hamster ovary (CHO) cells.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

70 mg erenumab in 1.0 mL (70 mg/mL) solution

140 mg erenumab in 1.0 mL (140 mg/mL) solution

3. PHARMACEUTICAL FORM

Solution for injection, for subcutaneous use.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

AIMOVIG is indicated for prophylaxis of migraine in adults.

4.2 Dosage and Administration

4.2.1 Dosage

The recommended dose of AIMOVIG is 70 mg administered once monthly.

Some patients may benefit from a dosage of 140 mg administered once monthly. See Clinical Data (5.1.1).

If AIMOVIG dose is missed, administer as soon as possible. Thereafter, AIMOVIG can be scheduled monthly from the date of the last dose.

4.2.2 Method of Administration

AIMOVIG is administered subcutaneously.

AIMOVIG is intended for patient self-administration.

Administration should be performed by an individual who has been trained to administer the product. To administer the 140 mg dose, give two consecutive subcutaneous injections of 70 mg each of AIMOVIG, or a single subcutaneous injection of 140 mg.

For detailed instructions on storage, handling and administration, follow the directions provided in the “Instructions for Use and Handling (6.6).”

Important Administration Instructions

- Visually inspect AIMOVIG for particles and discoloration. AIMOVIG is a clear to opalescent, colorless to light yellow solution. Do not use if the solution is cloudy or discolored or contains flakes or particles.
- Administer AIMOVIG subcutaneously in the abdomen, thigh, or upper arm. If you want to use the same injection site, make sure it is not the same spot you used for a previous injection. Do not inject into areas where the skin is tender, bruised, red, or hard.
- Both the prefilled syringe and the prefilled SureClick® autoinjector/pen are for single use and designed to deliver the entire contents with no residual content.
- The needle shield within the white or orange cap of the prefilled autoinjector and the gray needle cap of the prefilled syringe contain dry natural rubber (a derivative of latex), which may cause allergic reactions in individuals sensitive to latex.

4.3 Contraindications

Aimovig is contraindicated in patients with serious hypersensitivity to erenumab or to any of the excipients. [See Special Warnings (4.4) and Precautions for Use, Adverse Reactions (4.8)].

4.4 Special Warnings and Precautions for Use

Hypersensitivity Reactions

Serious hypersensitivity reactions, including rash, angioedema, and anaphylactoid reactions, have been reported with Aimovig in post-marketing experience. These reactions may occur within minutes, although some may occur more than one week after treatment. If a serious or severe hypersensitivity reaction occurs, discontinue administration of Aimovig and initiate appropriate therapy. [See Contraindications (4.3)].

Constipation with Serious Complications

Constipation with serious complications has been reported with Aimovig in post-marketing experience. In a majority of cases, the onset was reported after the first dose of Aimovig treatment; however, patients also experienced events later in treatment. Many cases occurred in patients with a history of constipation or concurrent use of medications associated with decreased gastrointestinal motility. In some severe cases, hospitalization was required, including cases where surgery was necessary.

Monitor patients treated with Aimovig for severe constipation and manage as clinically appropriate. Advise patients to seek medical attention if they develop severe constipation.

Hypertension

Development of hypertension and worsening of pre-existing hypertension have been reported following the use of AIMOVIG in the post-marketing setting. Many of the patients had pre-existing hypertension or risk factors for hypertension. There were cases requiring pharmacological treatment and, in some cases, hospitalisation.

Monitor patients treated with AIMOVIG for new-onset hypertension, or worsening of pre-existing hypertension, and consider whether discontinuation of AIMOVIG is warranted if evaluation fails to establish an alternative etiology.

4.5 Interactions with Other Medicinal Products and Other Forms of Interaction

In an open-label, pharmacokinetic drug interaction study of AIMOVIG and a combined oral contraceptive in healthy female subjects, erenumab (140 mg subcutaneous [SC], single- dose) did not affect the pharmacokinetics of a combined oral contraceptive containing ethinyl estradiol and norgestimate.

In a randomized, double-blind, placebo-controlled study in healthy volunteers, concomitant administration of erenumab (140 mg intravenous [IV], single-dose) with sumatriptan had no effect on resting blood pressure compared with sumatritpan alone. AIMOVIG had no effect on the pharmacokinetics of sumatriptan.

Erenumab is not metabolized by cytochrome P450 enzymes and is unlikely to cause marked changes in pro-inflammatory cytokines that may impact cytochrome P450 enzyme expression or activity. As a result, interactions with concomitant medications that are substrates, inducers, or inhibitors of cytochrome P450 enzymes are unlikely.

4.5.1 Interference with Laboratory and Diagnostic Tests

Interference of AIMOVIG with laboratory and/or diagnostic tests has not been studied.

4.6 Special Populations

4.6.1 Pregnancy

There are no adequate and well-controlled studies on the use of AIMOVIG in pregnant women. In a cynomolgus monkey reproduction study, there were no effects on pregnancy, embryo-fetal or post-natal development (up to six months of age) when erenumab was dosed throughout pregnancy at exposure levels 40 or 17-fold higher than those achieved in patients receiving erenumab at the 70 or 140 mg once monthly dosing regimen, respectively based on area under the concentration curve (AUC). Measurable erenumab serum concentrations were observed in the infant monkeys at birth, confirming that erenumab, like other IgG antibodies, crosses the placental barrier.

Animal studies are not always predictive of human response and therefore, it is not known whether AIMOVIG can cause fetal harm when administered to a pregnant woman. AIMOVIG should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

4.6.2 Lactation

It is not known whether AIMOVIG is present in human milk. There are no data on the effects of AIMOVIG on the breastfed child or the effects of AIMOVIG on milk production. Because drugs are excreted in human milk and because of the potential for adverse effects in nursing infants from AIMOVIG, a decision should be made whether to discontinue nursing or discontinue AIMOVIG, taking into account the potential benefit of AIMOVIG to the mother and the potential benefit of breast feeding to the infant.

4.6.3 Fertility

No data are available on the effect of AIMOVIG on human fertility. There were no adverse effects on surrogate markers of fertility (anatomic pathology or histopathology changes in reproductive organs) in sexually mature monkeys at systemic exposures up to 283 or 123-fold higher than the clinical dose of 70 or 140 mg once monthly, respectively, based on serum AUC. [See Preclinical Safety Data/Nonclinical Toxicology (5.3)].

4.6.4 Pediatrics

The safety and effectiveness of AIMOVIG has not been studied in pediatric patients.

4.6.5 Geriatrics

AIMOVIG has not been studied in elderly patients aged 65 years of age and over. The pharmacokinetics of erenumab are not affected by age. [See Pharmacokinetic properties (5.2)].

4.6.6 Hepatic Impairment

No clinical studies have been performed in patients with hepatic impairment. Erenumab, as a human monoclonal antibody, is not metabolised by cytochrome P450 enzymes and hepatic clearance is not a major clearance pathway for erenumab.

4.6.7 Renal Impairment

No dose adjustment is necessary in patients with mild to moderate renal impairment. Population pharmacokinetic analysis of integrated data from the AIMOVIG clinical trials did not reveal a difference in the pharmacokinetics of erenumab in patients with mild or moderate renal impairment relative to those with normal renal function. Patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) have not been studied.

4.7 Effects on Ability to Drive and Use Machines

AIMOVIG is expected to have no influence on the ability to drive and use machines.

4.8 Adverse Reactions

4.8.1 Summary of the Safety Profile

Data from two phase 3 and two phase 2 clinical studies in migraine were pooled to evaluate the safety of AIMOVIG in comparison to placebo up to 12 weeks after treatment initiation.

There were a total of 2656 patients (1613 AIMOVIG and 1043 placebo) in these studies. Of these, 893 subjects received 70 mg dose of AIMOVIG and 507 subjects received 140 mg dose of AIMOVIG.

The overall safety population including open-label extension phases with Aimovig consists of 2537 patients (3040.2 patient-years) who received at least one dose of Aimovig: 2280 patients were exposed for at least 6 months, 1320 patients were exposed for at least 12 months, and 217 patients were exposed through 5 years. The overall safety profile of Aimovig remained consistent through 5 years of long-term open-label treatment.

4.8.2 Tabulated Summary of Adverse Reactions

Table 1 summarizes all adverse reactions that occurred in AIMOVIG-treated patients during the 12-week placebo-controlled period of the pooled trials. Most Adverse Drug Reactions (ADR's) were mild or moderate in severity.

Table 1. Adverse Reactions with AIMOVIG

System Organ Class	Adverse Reaction Preferred Term	Frequency Category	Overall subject incidence at 70 mg (N = 893) n (%)	Overall subject incidence at 140 mg (N = 507) n (%)	Nature/ Severity/ Seriousness
General disorders and administration site conditions	Injection site reactions[a]	Common	50 (5.6)[a]	23 (4.5)[a]	
Gastrointestinal disorders	Constipation	Common	12 (1.3)	16 (3.2)	
Musculoskeletal and connective tissue disorders	Muscle spasm	Common	1 (0.1)	10 (2.0)	One Grade 3 (0.2%) event was reported; all others were Grade 1-2.[c]
Skin and subcutaneous tissue disorders	Pruritus[b]	Common	6 (0.7)[b]	9 (1.8)[b]	

Note: Frequency is provided by CIOMS category (e.g., Very Common (≥ 10%), Common (≥ 1% and < 10%), Uncommon (≥ 0.1% and < 1%), Rare (≥ 0.01% and < 0.1%), Very Rare (< 0.01%)).

[a] Injection site reactions includes multiple preferred terms, such as injection site pain and injection site erythema.

[b] Pruritus includes preferred terms of generalized pruritus, pruritus, and pruritic rash.

[c] Severity grades are based on the Common Terminology Criteria for Adverse Events (CTCAE). Grade 1 Mild; Grade 2 Moderate; Grade 3 Severe or medically significant; Grade 4 Life-threatening consequences; Grade 5 Death.

4.8.3 Description of Selected Adverse Reactions

Injection site reactions

In the integrated 12-week placebo controlled period of studies, in subjects treated with AIMOVIG the most frequent injection site reactions were injection site pain, injection site erythema, and injection site pruritus. A majority of injection site reactions were Grade 1 in severity (mild) and transient. Injection site pain typically subsided within 1 hour after administration. One subject treated with Aimovig 70 mg SC discontinued due to injection site rash and no subject treated with AIMOVIG 140 mg SC discontinued due to injection site reactions in the 12-week placebo-controlled period of studies.

Constipation

In the integrated 12-week placebo-controlled period of studies, 28 cases of constipation were reported out of 1400 Aimovig-treated patients. All were mild or moderate severity. A majority of the cases (23) had onset within one month after the first dose; however, some patients also presented with constipation later on in treatment. In most cases (18), constipation resolved within three months. All but one case continued treatment.

4.8.4 Post-Marketing Experience

Immune system disorders

- Hypersensitivity reactions including rash, angioedema, and anaphylactoid reactions. [See Special Warnings and Precautions for Use (4.4)].

Gastrointestinal disorders

- Constipation with serious complications [see Special Warnings and Precautions for Use (4.4)]
- Oral sores (e.g., stomatitis, mouth ulceration, oral mucosal blistering).

Skin and subcutaneous tissue disorders

- Alopecia.
- Rash (e.g., rash papular, exfoliative rash, rash erythematous, urticaria, blister).

Vascular disorders

- Hypertension.

4.8.5 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The immunogenicity of AIMOVIG has been evaluated using an immunoassay for the detection of binding anti-erenumab antibodies. For patients whose sera tested positive in the screening immunoassay, an *in vitro* biological assay was performed to detect neutralizing antibodies.

During the double-blind treatment phase of the four migraine prophylaxis efficacy studies [20120178, 20120295, 20120296 and 20120297], the incidence of anti-erenumab antibody development was 6.3% (56/884) among subjects receiving the 70 mg dose of Aimovig (3 of whom had in vitro neutralizing activity) and 2.6% (13/504) among subjects receiving the 140 mg dose of Aimovig (none of whom had in vitro neutralizing activity). Including overall data from the 4 studies through the open-label extension, the incidence of anti-erenumab antibody development was 8.0% (185/2303) among patients who only received 70 mg or 140 mg of Aimovig throughout the entire study (8 of whom had in vitro neutralizing activity). There was no impact of anti-erenumab antibody development on efficacy or safety of Aimovig.

The incidence of anti-drug antibodies (ADAs) is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to erenumab with the incidence of antibodies to other products may be misleading.

4.9 Overdose

There is no experience with overdose in clinical trials with AIMOVIG. Doses up to 280 mg SC have been administered in clinical trials with no evidence of dose limiting toxicity.

In the event of an overdose, the patient should be treated symptomatically and supportive measures instituted as required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of Action

Erenumab is a human monoclonal antagonist antibody against the CGRP receptor with no significant pharmacological activity at adrenomedullin, calcitonin, and amylin receptors and lacks agonist activity at the CGRP receptor.

CGRP is a neuropeptide that modulates nociceptive signaling and a vasodilator that has been associated with migraine pathophysiology. In contrast with other neuropeptides, CGRP levels have been shown to increase significantly during migraine and return to normal with headache relief. Intravenous infusion of CGRP induces migraine-like headache in patients suggesting that CGRP may play a causal role in migraine.

The CGRP receptor is located at sites that are relevant to migraine pathophysiology. Erenumab potently and specifically competes with the binding of CGRP and inhibits its function at the CGRP receptor.

Pharmacodynamic Effects

In a randomized, double-blind, placebo-controlled study (20140254) to evaluate the effect of AIMOVIG (140 mg IV, single dose) in patients with stable angina, AIMOVIG did not decrease exercise duration during a treadmill test compared to placebo and did not aggravate myocardial ischemia in these patients.

5.1.1 Clinical Data

AIMOVIG was evaluated for prophylaxis of migraine in three pivotal studies across the spectrum of episodic and chronic migraine. Studies enrolled patients with a history of migraine, with or without aura according to the International Classification of Headache Disorders (ICHD-III) diagnostic criteria. Patients with pre-existing myocardial infarction, stroke, transient ischaemic attacks, unstable angina, coronary artery bypass surgery or other re-vascularisation procedures within 12 months prior to screening were excluded. Patients with poorly controlled hypertension or BMI >40 were also excluded from Study 1.AIMOVIG treatment demonstrated statistically significant and clinically meaningful improvements from baseline compared to placebo for key efficacy outcomes.

Chronic Migraine

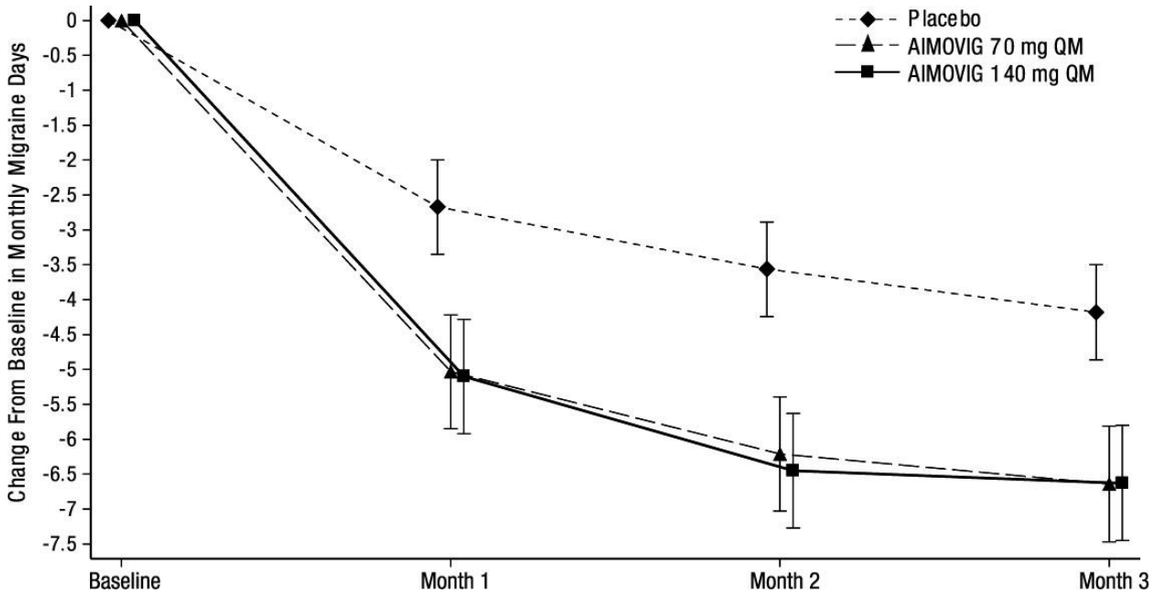
Study 1 (Study 20120295)

AIMOVIG was evaluated for prophylaxis of chronic migraine in a randomized, multi-center, 12-week, placebo-controlled, double-blind study. A total of 667 patients with a history of migraine with or without aura (≥ 15 headache days per month with ≥ 8 migraine days per month) were randomized to receive placebo (n = 286), AIMOVIG 70 mg (n = 191) or AIMOVIG 140 mg (n = 190) subcutaneous injections monthly for 12 weeks. Randomization was stratified by region (North America vs. other) and the presence of acute medication overuse (present in 41% of overall patients) excluding patients with opioid overuse. The mean migraine frequency at baseline was approximately 18 migraine days per month and was similar across treatment groups. Patients were allowed to use acute headache treatments including triptans, ergotamine derivatives and NSAIDs during the study.

Patients had a median age of 43 years (range: 18 – 66 years), 83% were female and 94% were white. Patients could have failed (i.e. no therapeutic response) up to three previous prophylactic treatment categories due to lack of efficacy, while there was no limit to the number of previous failures for poor tolerability. Overall, in this study population, 68% had failed one or more previous prophylactic treatments due to lack of efficacy or poor tolerability, and 49% had failed two or more previous prophylactic treatments due to lack of efficacy or poor tolerability. In addition to excluding patients with opioid overuse, the study excluded patients with concurrent use of migraine prophylactic treatments. A total of 182 (96%) patients in the AIMOVIG 140 mg arm, 184 (96%) patients in the AIMOVIG 70 mg arm, and 265 (93%) patients in the placebo arm completed the study (completed week 12 assessment). Of the 23 (3.4%) patients who discontinued treatment, 2 patients in the AIMOVIG 140 mg-treated group, no patients in the AIMOVIG 70 mg-treated group and 2 patients in the placebo group discontinued due to adverse events.

The primary outcome measure was the change from baseline at month 3 in monthly migraine days. Secondary outcome measures included the achievement of 50-100% reduction in monthly migraine days from baseline (≥50% responders), change from baseline in monthly acute migraine-specific medication days, and change from baseline in cumulative monthly headache hours. Other than for cumulative monthly headache hours, AIMOVIG treatment demonstrated statistically significant and clinically meaningful improvements from baseline at month 3 compared to placebo for efficacy outcomes as summarized in Figure 1 and Table 2. Reduction in mean monthly migraine days from placebo were observed in a monthly analysis from month 1 and in a follow-up weekly analysis an onset of AIMOVIG effect was seen from the first week of administration.

Figure 1: Change From Baseline in Monthly Migraine Days in Study 1[a]



[a] Least-square means and 95% confidence intervals are presented.
The p-value for the difference in least-square means between erenumab and placebo assessed at Month 3 (primary outcome measure) was < 0.001 for both AIMOVIG dose groups.

Table 2. Efficacy Outcomes in Study 1 at Month 3

	AIMOVIG 70 mg (n = 188)	AIMOVIG 140 mg (n = 187)	Placebo (n = 281)	Treatment Difference/ Odds Ratio	p-value[a]
Efficacy Outcomes					
Monthly migraine days (MMD)					
Mean change[b] 95% CI	-6.64 (-7.47, -5.81)	-6.63 (-7.45, -5.80)	-4.18 (-4.86, -3.50)	70 mg: -2.46 (-3.52, -1.39) 140 mg: -2.45 (-3.51, -1.38)	Both < 0.001
≥ 50% MMD responders					
%	39.9	41.2	23.5		
Odds ratio[c]				70 mg:	Both < 0.001

95% CI				2.18 (1.46, 3.27) 140 mg: 2.34 (1.56, 3.51)	
≥ 75% MMD responders[d]					
%	17.0	20.9	7.8		n/a
Odds ratio 95% CI				70 mg: 2.43 (1.36, 4.33) 140 mg: 3.13 (1.78, 5.48)	
Monthly acute migraine-specific medication days[e]					
Mean change[b] 95% CI	-3.45 (-4.02, -2.87)	-4.13 (-4.70, -3.56)	-1.58 (-2.05, -1.11)	70 mg: -1.86 (-2.60, -1.13) 140 mg: -2.55 (-3.28, -1.82)	Both < 0.001
Cumulative headache hours					
Mean change[b] 95% CI	-64.76 (-78.34, -51.17)	-74.53 (-88.05, -61.01)	-55.22 (-66.38, -44.06)	70 mg: -9.54 (-26.98, 7.90) 140 mg: -19.31 (-36.71, -1.92)	ns
Patient-reported outcome measures					
HIT-6					
Mean change[f] 95% CI	-5.6 (-6.5, -4.6)	-5.6 (-6.5, -4.6)	-3.1 (-3.9, -2.3)	70 mg: -2.5 (-3.7, -1.2) 140 mg: -2.5(-3.7, -1.2)	n/a
MIDAS total					
Mean change[f] 95% CI	-19.41 (-25.19, -13.62)	-19.76 (-25.56, -13.97)	-7.54 (-12.40, -2.69)	70 mg: -11.86 (-19.34, -4.39) 140 mg: -12.22 (-19.64, -4.75)	n/a

CI = confidence interval; HIT = Headache impact test; MIDAS = Migraine disability assessment; n/a = not applicable; MMD = monthly migraine days; ns = not significant.

a. All p-values are reported as unadjusted p-values and are statistically significant after adjustment for multiple comparisons.

b. LS mean change from baseline at month 3, treatment difference, and p-value are based on a linear mixed effects model including treatment group, baseline monthly value, stratification factors (region [North America vs. Europe] and medication overuse [presence vs. absence]), scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data.

c. Odds ratio and p-value for ≥ 50% responders at month 3 are based on a stratified Cochran-Mantel-Haenszel test after missing data were imputed as non-response.

d. Post-hoc analysis; no hypothesis testing was performed.

e. Migraine specific medications include triptans and ergotamine derivatives.

f. Change and reduction from baseline were evaluated at the last 4 weeks of the 12-week double-blind treatment phase.

Based on a pre-specified analysis, AIMOVIG 70 mg and 140 mg were efficacious in patients who had previously been treated with migraine prophylactics. Table 3 provides subgroup results of Study 1 based on prior prophylactic failure(s) due to lack of efficacy or intolerance, in a pre-specified analysis.

Table 3. Efficacy Outcomes in Study 1 at Month 3 in Subgroups Based on Prior Prophylactic Failure

	Aimovig 70 mg (patients never failed/failed ≥1 medication/failed ≥2 medications, n=64/124/90)	Aimovig 140 mg (patients never failed/failed ≥1 medication/failed ≥2 medications, n=62/125/92)	Placebo (patients never failed/failed ≥1 medication/failed ≥2 medications, n=84/197/141)	Treatment difference / Odds ratio (95% CI)
Monthly migraine days (MMD)[a] - Mean change[b] (95% CI)				TD
Never failed	-7.86 (-9.33, -6.39)	-6.14 (-7.61, -4.66)	-5.67 (-6.98, -4.36)	70 mg: -2.19 (-4.10, -0.28) 140 mg: -0.47 (-2.39, 1.46)
Failed ≥1 medication	-5.98 (-6.99, -4.97)	-6.84 (-7.84, -5.85)	-3.51 (-4.33, -2.70)	70 mg: -2.47 (-3.76, -1.18) 140 mg: -3.33 (-4.61, -2.06)
Failed ≥2 medications	-5.38 (-6.56, -4.20)	-6.96 (-8.10, -5.82)	-2.68 (-3.63, -1.72)	70 mg: -2.71 (-4.20, -1.21) 140 mg: -4.28 (-5.75, -2.80)
≥50% MMD responders[c] - %				OR[d]
Never failed	50%	41.9 %	38.1 %	70 mg: 1.75 (0.89, 3.43) 140 mg: 1.33 (0.67, 2.66)
Failed ≥1 medication	34.7%	40.8 %	17.3 %	70 mg: 2.64 (1.56, 4.48) 140 mg: 3.30 (1.98, 5.51)
Failed ≥2 medications	35.6%	41.3 %	14.2 %	70 mg: 3.46 (1.81, 6.61) 140 mg: 4.18 (2.21, 7.91)
Monthly acute migraine-specific medication days[e] - Mean change[b] (95% CI)				TD
Never failed	-2.48 (-3.31, -1.64)	-2.48 (-3.31, -1.64)	-1.78 (-2.52, -1.05)	70 mg: -0.69 (-1.77, 0.38) 140 mg: -0.69 (-1.78, 0.39)
Failed ≥1 medication	-3.83 (-4.58, -3.08)	-4.90 (-5.64, -4.16)	-1.47 (-2.07, -0.87)	70 mg: -2.36 (-3.31, -1.41) 140 mg: -3.43 (-4.37, -2.49)
Failed ≥2 medications	-4.05 (-4.96, -3.15)	-5.39 (-6.27, -4.51)	-1.26 (-2.00, -0.53)	70 mg: -2.79 (-3.94, -1.65) 140 mg: -4.13 (-5.26, -3.00)

CI = confidence interval; MMD = monthly migraine days; TD = treatment difference; OR = odds ratio

a. MMD at baseline was approximately 18 migraine days per month and similar across the above subgroups.

b. LS mean change from baseline at Month 3 and treatment difference are based on a linear mixed effects model including treatment group, baseline monthly value, stratification factors (region [North America versus other and medication overuse [presence versus absence]), scheduled visit and the interaction of treatment group with scheduled visit, without any imputation for missing data.

c. Responders are defined as patients who achieve ≥50% reduction on MMD from baseline.

d. Odds ratio for ≥50% responders at Month 3 based on a stratified Cochran-Mantel-Haenszel test after missing data were imputed as non-response.

e. Migraine-specific medications include triptans and ergotamine derivatives.

In patients with medication overuse (41% of the total population in Study 1), efficacy was observed with 70 mg and 140 mg AIMOVIG compared to placebo for monthly migraine days (LSM (95% CI) 70 mg: -3.10 days (-4.83, -1.37); 140 mg: -3.10 days (-4.81, -1.39); 50% responders: 34.6% for 140 mg, 36.4% for 70 mg versus 17.7% for placebo), with odds ratio (95% CI) 70 mg: 2.67 (1.36, 5.22); 140 mg: 2.51 (1.28, 4.94) and in acute migraine-specific medication days (LSM (95% CI) 70 mg: -3.33 (-4.72, -1.94); 140 mg: -2.79 (-4.16, -1.42)).

Improvement in functional ability was assessed by the Headache Impact Test (HIT-6) and the Migraine Disability Assessment (MIDAS) questionnaires. Mean change from baseline to Month 3 compared to placebo for the patient reported outcome measures are summarized in Table 2. The established between-group Minimally Important Difference (MID) for the reduction in HIT-6 total score is 2.3.

Efficacy was sustained for up to 1 year in the open-label extension of Study 1 in which patients received 70 mg and/or 140 mg AIMOVIG. 74.1% of patients completed the 52-week extension. Pooled across the two doses, a reduction of -9.3 MMD was observed after 52 weeks relative to core study baseline. 59% of patients completing the study achieved a 50% response in the last month of the study.

Episodic Migraine

Study 2 (Study 20120296, STRIVE)

Study 2 was a randomized, multi-center, 24-week, placebo-controlled, double-blind study evaluating AIMOVIG for prophylaxis of episodic migraine. A total of 955 patients with history of migraine with or without aura for a duration of ≥ 12 months and 4-14 migraine days per month were randomized to receive either AIMOVIG 70 mg (n = 317), 140 mg (n = 319) or placebo (n = 319) by subcutaneous injection monthly for 6 months. Randomization was stratified by use of prophylactic medications (concomitant, prior use or no prior use) and region (North America vs. other). The mean migraine frequency at baseline was approximately 8 migraine days per month and was similar

across treatment groups. Patients were allowed to use acute headache treatments including triptans, ergotamine derivatives and NSAIDs during the study.

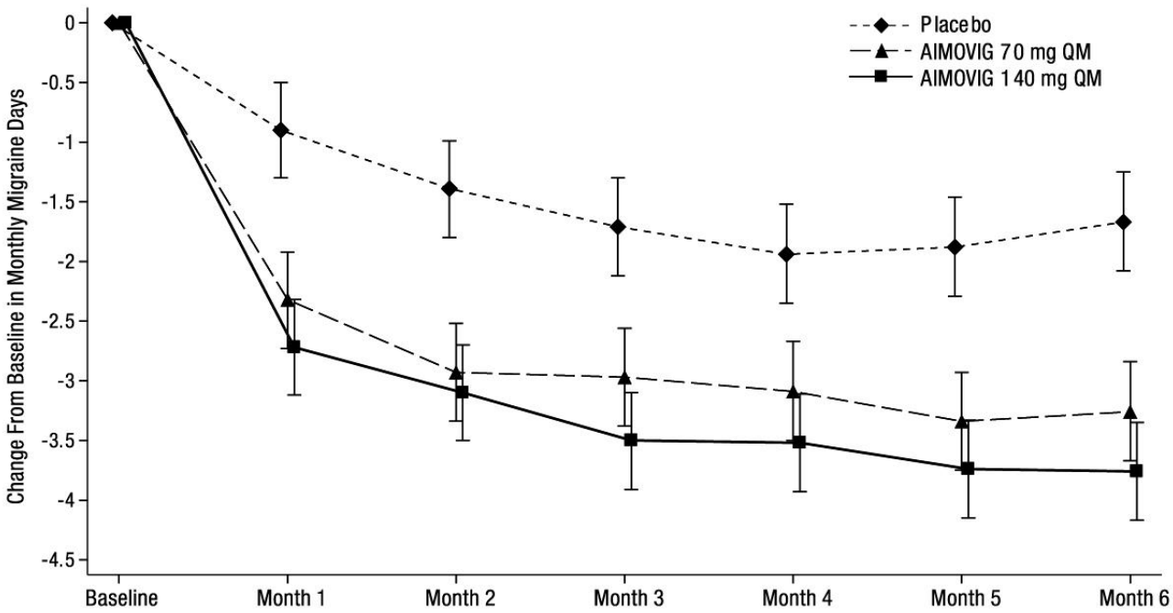
Patients had a median age of 42 years (range: 18 – 65 years); 85% were female and 89% were white. Patients could have failed to respond up to two previous prophylactic treatments. The study excluded patients with medication overuse. Overall, 865 (90.6%) patients completed the double-blind phase, including 287 (90.5%) in the 70 mg group, 294 (92.2%) in the 140 mg group, 284 (89.0%) in the placebo group. Of the 87 (9.1%) patients who discontinued treatment, 7 patients in the 70 mg AIMOVIG group, 6 patients in the 140 mg AIMOVIG group and 7 patients in the placebo group discontinued due to adverse events.

The primary outcome measure was the change from baseline during months 4-6 in monthly migraine days. Secondary outcome measures included the achievement of a 50-100% reduction in mean monthly migraine days from baseline (≥ 50% responders), change from baseline in mean monthly acute migraine-specific medication days and change from baseline in the 2 Migraine Physical Function Impact Diary (MPFID) domains scores: physical impairment (PI) and impact on everyday activities (EA). The Migraine Physical Function Impact Diary (MPFID) is a patient reported outcomes instrument that measures the impact of migraine on physical functioning. It contains 13 items evaluating the impact of migraine during the previous 24 hours on two physical functioning concepts of interest: impact on everyday activities (EA; 7 items: e.g., difficulty doing activities requiring concentration), physical impairment (PI, 5 items: e.g., difficulty doing activities requiring physical effort) and one global item assessing the overall impact on everyday activities. Patients rate the duration of impact or level of difficulty associated with migraine on a daily basis. Monthly MPFID scores are averaged over days with and without migraine; higher scores indicate worse impact on the EA and PI domains.

AIMOVIG treatment demonstrated statistically significant and clinically meaningful improvements from baseline during months 4-6 compared to placebo for efficacy outcomes as summarized in Figure 2 and Table 4. Differences from placebo were observed as early as month 1.

Based on a pre-specified analysis, AIMOVIG 70 mg and 140 mg were efficacious in patients who had previously been treated with migraine prophylactics. Table 5 provides subgroup results of Study 2 based on prior prophylactic failure due to lack of efficacy or intolerance, in a pre-specified analysis.

Figure 2: Change From Baseline in Monthly Migraine Days in Study 2[a]



[a] Least-square means and 95% confidence intervals are presented.
The p-value for the difference in least-square means between erenumab and placebo assessed as the average over Months 4, 5, and 6 (primary outcome measure) was < 0.001 for both AIMOVIG dose groups.

Table 4: Efficacy Outcomes at Months 4-6 in Study 2

	AIMOVIG 70 mg (n = 312)	AIMOVIG 140 mg (n = 318)	Placebo (n = 316)	Treatment Difference/ Odds Ratio	p-value[a]
Efficacy Outcomes					
Monthly migraine days (MMD)					
Mean change[b] 95% CI	-3.23 (-3.58, -2.88)	-3.67 (-4.02, -3.33)	-1.83 (-2.18, -1.48)	70 mg: -1.40 (-1.88, -0.92) 140 mg: -1.85 (-2.33, -1.37)	Both < 0.001
≥ 50% MMD responders					
%	43.3	50.0	26.6		
Odds ratio[c] 95% CI				70 mg: 2.13 (1.52, 2.98) 140 mg: 2.81 (2.01, 3.94)	Both < 0.001
≥ 75% MMD responders[d]					
%	20.8	22.0	7.9		n/a
Odds ratio 95% CI				70 mg: 3.14 (1.91, 5.18) 140 mg: 3.35 (2.05, 5.49)	
Monthly acute migraine-specific medication days[e]					
Mean change[b] 95% CI	-1.13 (-1.34, -0.92)	-1.61 (-1.83, -1.40)	-0.20 (-0.41, 0.02)	70 mg: -0.94 (-1.23, -0.64) 140 mg: -1.42 (-1.71, -1.12)	Both < 0.001
Patient-reported outcome measures					
MPFID physical impairment domain					
Mean change[b] 95% CI	-4.24 (-5.02, -3.45)	-4.81 (-5.59, -4.03)	-2.38 (-3.16, -1.59)	70 mg: -1.86 (-2.95, -0.77) 140 mg: -2.43 (-3.51, -1.35)	Both < 0.001
MPFID impact on everyday activities domain					
Mean change[b] 95% CI	-5.52 (-6.28, -4.75)	-5.86 (-6.62, -5.10)	-3.30 (-4.06, -2.53)	70 mg: -2.22 (-3.28, -1.16) 140 mg: -2.57 (-3.62, -1.51)	Both < 0.001
HIT-6					

Mean change 95% CI	-6.7 (-7.4, -6.0)	-6.9 (-7.6, -6.3)	-4.6 (-5.3, -4.0)	70 mg: -2.1 (-3.0, -1.1) 140 mg: -2.3 (-3.2, -1.3)	n/a
MIDAS (modified) total					
Mean change 95% CI	-6.7 (-7.6, -5.9)	-7.5 (-8.3, -6.6)	-4.6 (-5.5, -3.8)	70 mg: -2.1 (-3.3, -0.9) 140 mg: -2.8 (-4.0, -1.7)	n/a
Response on MPFID-physical impairment domain					
Percentage (%)[f]	39.1	42.5	30.1		
Odds Ratio 95% CI				70 mg: 1.49 (1.07, 2.08) 140 mg: 1.73 (1.24, 2.40)	
Response on MPFID-impact on everyday activities domain					
Percentage (%)[f]	49.0	50.3	34.5		
Odds Ratio 95% CI				70 mg: 1.83 (1.33, 2.52) 140 mg: 1.93 (1.40, 2.67)	

CI = confidence interval; HIT = Headache impact test; MIDAS = Migraine disability assessment; n/a = not applicable; MMD = monthly migraine days; MPFID = Migraine Physical Function Impact Diary; ns = not significant.

a. All p-values are reported as unadjusted p values and are statistically significant after adjustment for multiple comparisons.

b. LS mean change from baseline at month 4-6, treatment difference, and p-value are based on a linear mixed effects model including treatment group, baseline value, stratification factors (region [North America vs. rest of world] and prior prophylactic medication use [naïve, prior use only, concurrent use]), scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data.

c. Odds ratio and p-value for ≥ 50% responders at month 4-6 are based on a stratified Cochran-Mantel-Haenszel test after missing data were imputed as non-response.

d. Post-hoc analysis; no hypothesis testing was performed.

e Migraine-specific medications include triptans and ergotamine derivatives.

f. Reduction from baseline in PI, EA average monthly domain score >=5.

Table 5. Efficacy Outcomes at Month 4-6 in Subgroups Based on Prior Prophylactic Failure in Study 2

	AIMOVIG 70 mg (patients never failed/failed ≥1 medication, n=185/127)	**AIMOVIG 140 mg (patients never failed/failed ≥1 medication, n=202/116)**	**Placebo (patients never failed/failed ≥1 medication, n=190/126)**	**Treatment difference / Odds ratio (95% CI)**
Monthly migraine days (MMD)[a] - Mean change[b] (95% CI)				TD
Never failed	-3.26 (-3.83, -2.70)	-3.63 (-4.15, -3.10)	-2.32 (-2.87, -1.78)	70 mg: -0.94 (-1.54, -0.34) 140 mg: -1.30 (-1.89, -0.71)
Failed ≥1 medication	-2.64 (-3.34, -1.94)	-3.15 (-3.89, -2.42)	-0.62 (-1.32, 0.08)	70 mg: -2.02 (-2.81, -1.23) 140 mg: -2.54 (-3.35, -1.72)
≥50% MMD responders[c] - %				OR[d]
Never failed	46.5%	55.9%	32.6%	70 mg: 1.77(1.16, 2.69) 140 mg: 2.66 (1.76, 4.02)
Failed ≥1 medication	38.6%	39.7%	17.5%	70 mg: 2.93 (1.63, 5.27) 140 mg: 3.06 (1.70, 5.52)
Monthly acute migraine-specific medication days[e] - Mean change[b] (95% CI)				TD
Never failed	-0.91 (-1.20, -0.61)	-1.27 (-1.55, -0.99)	-0.33 (-0.62, -0.04)	70 mg: -0.57 (-0.89, -0.25) 140 mg: -0.94 (-1.25, -0.63)
Failed ≥1 medication	-1.51 (-2.00, -1.01)	-2.16 (-2.68, -1.65)	-0.05 (-0.54, 0.45)	70 mg: -1.46 (-2.02, -0.91) 140 mg: -2.12 (-2.69, -1.55)

CI = confidence interval; MMD = monthly migraine days; TD = treatment difference; OR = odds ratio

a. MMD at baseline was approximately 8 migraine days per month and similar across the above subgroups.

b. LS mean change from baseline at Month 4-6 and treatment difference are based on a linear mixed effects model including treatment group, baseline monthly value, stratification factors (region [North America versus other] and medication overuse [presence vs absence]), scheduled visit and the interaction of treatment group with scheduled visit, without any imputation for missing data.

c. Responders are defined as patients who achieve ≥50% reduction on MMD from baseline.

d. Odds ratio for ≥50% responders at Month 4-6 based on a stratified Cochran Mantel Haenszel test after missing data were imputed as non-response.

e. Migraine specific medications include triptans and ergotamine derivatives.

Efficacy was sustained up to 1 year in the active re-randomisation part of Study 2. Patients were re-randomised in the Active Treatment Phase (ATP) to 70 mg or 140 mg AIMOVIG. 79.8% completed the entire study out to 52 weeks. The reduction in monthly migraine days from baseline to Week 52 was -4.22 in the 70 mg ATP group and -4.64 days in the 140 mg ATP group. At Week 52, the proportion of subjects who achieved a ≥50% reduction in MMD from baseline was 61.0% in the 70 mg ATP and 64.9% in the 140 mg ATP group.

Study 3 (Study 20120297, ARISE)

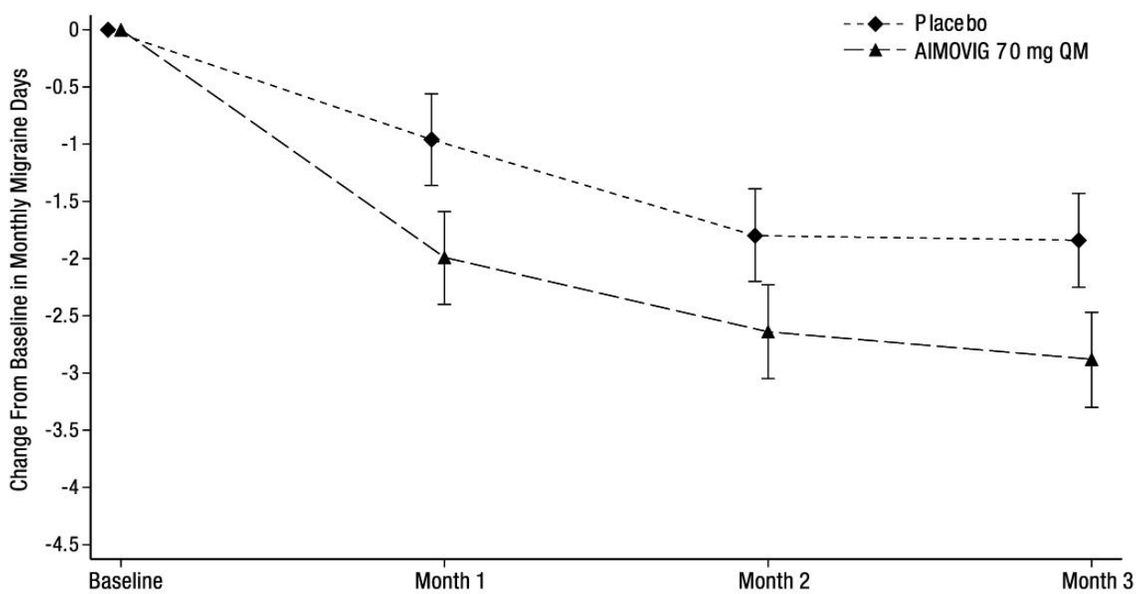
Study 3 was a randomized, multi-center, 12-week, placebo-controlled, double-blind study evaluating AIMOVIG for prophylaxis of episodic migraine. A total of 577 patients with history of migraine with or without aura for a duration of ≥ 12 months and 4-14 migraine days per month were randomized to receive either AIMOVIG 70 mg (n = 286) or placebo (n = 291) by subcutaneous injection monthly. Randomization was stratified by use of prophylactic medications (concomitant, prior use or no prior use) and region (North America vs. other). The mean migraine frequency at baseline was approximately 8 migraine days per month and was similar across treatment groups. Patients were allowed to use acute headache treatments including triptans, ergotamine derivatives and NSAIDs during the study.

Patients had a median age of 43 years (range: 18 – 65 years), 85% were female and 90% were white. Patients could have failed to respond up to two previous prophylactic treatments. The study excluded patients with medication overuse. Overall, 546 (94.6%) patients completed the double-blind phase, including 271 (94.8) receiving AIMOVIG 70 mg and 275 (94.5) receiving placebo. Of the 31 (5.4%) patients who discontinued treatment, 15 patients receiving AIMOVIG 70 mg and 1 patients receiving placebo discontinued due to adverse events.

The primary outcome measure was the change from baseline in monthly migraine days. Secondary outcome measures included the achievement of a 50-100% reduction in mean monthly migraine days from baseline (≥ 50% responders), change from baseline in mean monthly acute migraine-specific medication days and 5-point reduction from baseline in the two Migraine Physical Function Impact Diary (MPFID) domains scores: physical impairment (PI) and impact on everyday activities (EA). The Migraine Physical Function Impact Diary (MPFID) is a patient reported outcomes instrument that measures the impact of migraine on physical functioning. It contains 13 items evaluating the impact of migraine during the previous 24 hours on two physical functioning concepts of interest: impact on everyday activities (EA; 7 items: e.g., difficulty doing activities requiring concentration), physical impairment (PI, 5 items: e.g., difficulty doing activities requiring physical effort) and one global item assessing the overall impact on everyday activities. Patients rate the duration of impact or level of difficulty associated with migraine on a daily basis. Monthly MPFID scores are averaged over days with and without migraine; higher scores indicate worse impact on the EA and PI domains.

AIMOVIG treatment demonstrated statistically significant and clinically meaningful improvements from baseline compared to placebo for efficacy outcomes as shown in Figure 3 and Table 6.

Figure 3: Change from Baseline in Monthly Migraine Days in Study 3[a]



[a] Least-square means and 95% confidence intervals are presented.

Table 6: Efficacy Outcomes at Month 3 in Study 3

	Placebo (n = 288)	AIMOVIG 70 mg (n = 282)	Treatment Difference/ Odds Ratio	p-value[a]
Monthly Migraine Days (MMD)				
Mean change[b] 95% CI	-1.84 (-2.25, -1.43)	-2.88 (-3.30, -2.47)	-1.04 (-1.61, -0.47)	< 0.001
≥ 50% MMD responders				
%	29.5	39.7		
Odds ratio[c] 95% CI			1.59 (1.12, 2.27)	0.010
≥ 75% MMD responders				
%	11.8	19.1		
Odds ratio[c] 95% CI			1.79 (1.12, 2.87)	0.015
Monthly acute migraine-specific medication days[e]				
Mean change[b] 95% CI	-0.62 (-0.89, -0.35)	-1.21 (-1.48, -0.94)	-0.59 (-0.96, -0.21)	0.002
MPFID physical impairment domain				
%	27.1	33.0		
Odds ratio[c] 95% CI			1.33 (0.92, 1.90)	0.13
MPFID impact on everyday activities domain				
%	35.8	40.4		
Odds ratio[c] 95% CI			1.22 (0.87, 1.71)	0.26

CI = confidence interval; MMD = monthly migraine days; MPFID = Migraine Physical Function Impact Diary.

a. All p-values are reported as unadjusted p-values and are statistically significant after adjustment for multiple comparisons.

b. LS mean change from baseline at month 3, treatment difference, and p-value are based on a linear mixed effects model including treatment group, baseline value, stratification factors (region [North America vs. rest of world] and prior prophylactic medication use [naïve, prior use only, concurrent use]), scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data.

c. Odds ratio and p-value for ≥ 50% responders at month 3 are based on a stratified Cochran-Mantel-Haenszel test after missing data were imputed as non-response

.

Table 7: Monthly Migraine Days (MMD) in Subgroups Based on Prior Prophylactic Failure in Study 3

	Placebo	Aimovig 70 mg	Treatment Difference/ Odds Ratio
Never failed			
N	174	167	
Mean baseline	8.19	7.80	
Mean change[a]	-1.84	-2.91	-1.07
95% CI	(-2.42, -1.26)	(-3.49, -2.32)	(-1.81, -0.33)
Failed ≥ 1 medication			
N	114	115	
Mean baseline	8.67	8.61	
Mean change[a]	-1.77	-2.79	-1.03
95% CI	(-2.65, -0.89)	(-3.70, -1.89)	(-1.93, -0.12)

CI = confidence interval; MMD = monthly migraine days.

a. LS mean change from baseline at month 3 and treatment difference are based on a linear mixed effects model including treatment group, baseline value, stratification factors (region [North America vs. rest of world] and prior prophylactic medication use [naïve, prior use only, concurrent use]), scheduled visit, and the interaction of treatment group with scheduled visit, without any imputation for missing data.

Study 4 (Study 20120178)

Study 4 was a phase 2, randomized, multi-center, 12-week, double-blind, placebo-controlled, study followed by a 256-week, open-label treatment phase evaluating Aimovig for prophylaxis of episodic migraine. In the double-blind treatment phase, a total of 483 patients were randomized to receive placebo, Aimovig 7 mg, 21 mg or 70 mg monthly, and 383 patients continued into the open-label treatment phase initially receiving Aimovig 70 mg (median exposure: 2.0 years), of which 250 patients increased their dose to 140 mg (median exposure: 2.7 years). Among those 250 patients, 214 (85.6%) patients completed the open-label treatment phase. Out of the 383 patients who

entered the 256-week, open-label treatment phase, the most common reasons for discontinuing Aimovig were patient request (84 patients, 21.9%), adverse events (19 patients, 5.0%), and lost to follow-up (14 patients, 3.7%).

Patients who entered the open-label treatment phase had a median age of 43 years (range: 18-60 years) at study baseline, 79% were female, and 92% were white. Baseline disease characteristics were consistent across the prior placebo and Aimovig treatment groups.

The long-term efficacy results are summarized for patients who increased their dose to 140 mg (Table 8).

Table 8. Summary of Efficacy Endpoints During the Open-label Treatment Phase in Patients Who Increased Aimovig Dose From 70 mg to 140 mg

	Monthly Migraine Days (MMD)	**Monthly Migraine-specific Medication Days (MSMD)**	**MMD Responders, n (%)**		
Study baseline[a], Mean (SE) (N1 = 250)	8.69 (0.17)	4.53 (0.23)			
	Change from study baseline, Mean (SE)		**≥ 50%**	**≥ 75%**	**100%**
Week 64[b] (Month 16) (N1 = 230)	-5.00 (0.27)	-2.56 (0.21)	151 (65.7)	97 (42.2)	58 (25.2)
Week 268[c] (Month 67) (N1 = 138)	-5.30 (0.33)	-3.16 (0.30)	98 (71.0)	65 (47.1)	49 (35.5)

All subjects received Aimovig 70 mg at week 64 and Aimovig 140 mg at week 268.
SE = standard error; N1 = number of patients with observed data; responder rate % = n/N1 * 100
[a] The baseline phase occurred prior to entry into the 12-week double-blind treatment phase.
[b] Clinical outcome assessments were collected daily using an eDiary during the first 52 weeks of the open-label treatment phase (up to the week 64 study visit).
[c] The daily eDiary collection was resumed for 4-week periods during weeks 189 to 192 and every 24 weeks thereafter until the end of the open-label treatment phase (up to week 268). At this point, some patients had completed the study or were past the time points for efficacy data collection.

5.2 Pharmacokinetic properties

Erenumab exhibits non-linear kinetics as a result of binding to CGRP receptor. Subcutaneous administration of a 70 mg and 140 mg dose in healthy volunteers resulted in a C_{max} mean (standard deviation [SD]) of 6.1 (2.1) mcg/mL and 15.8 (4.8) mcg/mL respectively and AUC_{last} mean (SD) of 159 (58) day*mcg/mL and 505 (139) day*mcg/mL respectively.

Less than 2-fold accumulation was observed in trough serum concentrations (C_{min} [SD] 5.7 [3.1] and 6.2 [2.9] mcg/mL for episodic and chronic migraine subjects, respectively following 70 mg doses; C_{min} [SD] 12.8 [6.53] and 14.9 [6.45] mcg/mL for episodic and chronic migraine subjects, respectively following 140 mg doses) administered subcutaneously every 4 weeks and serum trough concentrations approached steady state by 12 weeks of dosing. The effective half-life of AIMOVIG is 28 days.

Absorption

Following a single subcutaneous dose of 70 mg or 140 mg AIMOVIG administered to healthy adults, median peak serum concentrations were attained in approximately 6 days, and estimated absolute bioavailability was 82%.

Distribution

Following a single 140 mg intravenous dose, the mean (SD) volume of distribution during the terminal phase (V_z) was estimated to be 3.86 (0.77) L.

Metabolism and Excretion

Two elimination phases were observed for AIMOVIG. At low concentrations, the elimination is predominantly through saturable binding to target (CGRP-R), while at higher concentrations the elimination of AIMOVIG is largely through a non-specific, non-saturable proteolytic pathway.

Specific Populations

The pharmacokinetics of erenumab were not affected by age, gender, race, migraine subtype (episodic or chronic migraine), or creatinine clearance, across all approved populations based on population pharmacokinetics (PK) analysis.

5.3 Preclinical Safety Data/Nonclinical Toxicology

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with AIMOVIG. AIMOVIG is not pharmacologically active in rodents and has biologic activity in the cynomolgus monkeys, but this species is not an appropriate model for evaluation of tumorigenic risk. The mutagenic potential of AIMOVIG has not been evaluated; however, monoclonal antibodies are not expected to alter DNA or chromosomes.

Mating studies have not been conducted on AIMOVIG. There were no adverse effects on surrogate markers of fertility (anatomic pathology or histopathology changes in reproductive organs) in the chronic toxicology study in sexually mature monkeys subcutaneously administered AIMOVIG at dose levels up to 150 mg/kg twice weekly for 6 months, at systemic exposures up to 283 or 123-fold higher than the clinical dose of 70 mg or 140 mg once monthly, respectively, based on serum AUC.

Animal Toxicology

There were no adverse effects in monkeys dosed up to 150 mg/kg SC twice weekly for up to 6 months at systemic exposures up to 283 or 123-fold higher than the clinical dose of 70 or 140 mg once monthly, respectively, based on serum AUC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

70 mg per mL prefilled syringe, prefilled autoinjector/pen

- Sucrose: 73 mg/7.3% (w/v); NF, PhEur, JP
- Glacial acetic acid: 1.5 mg/25 mM; USP, PhEur, JP
- Polysorbate 80: 0.10 mg/0.010% (w/v); NF, PhEur, JP
- Water for injection
- Sodium hydroxide to pH of 5.2; NF, PhEur, JP

140 mg per mL prefilled syringe, prefilled autoinjector

- Sucrose: 65 mg/6.5% (w/v); NF, PhEur, JP
- Glacial acetic acid: 2.0 mg/34 mM; USP, PhEur, JP
- Polysorbate 80: 0.10 mg/0.010% (w/v); NF, PhEur, JP
- Water for injection
- Sodium hydroxide to pH of 5.2; NF, PhEur, JP

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf-life

36 months at 2°C to 8°C (36°F to 46°F)

6.4 Special Precautions for Storage

- Store refrigerated at 2°C to 8°C (36˚F to 46˚F) in the original carton to protect from light until time of use.

- If removed from the refrigerator, AIMOVIG should be kept at controlled room temperature (up to 25°C [77°F]) in the original carton and must be used within 7 days. Throw away AIMOVIG that has been left at room temperature for more than 7 days.
- Do not freeze.
- Do not shake.

6.5 Nature and Contents of Container

- Sterile, preservative-free solution, clear to opalescent; colorless to yellowish solution, practically free from particles.
- The needle shield within the white or orange cap of the prefilled autoinjector and the gray needle cap of the prefilled syringe contain dry natural rubber (a derivative of latex).

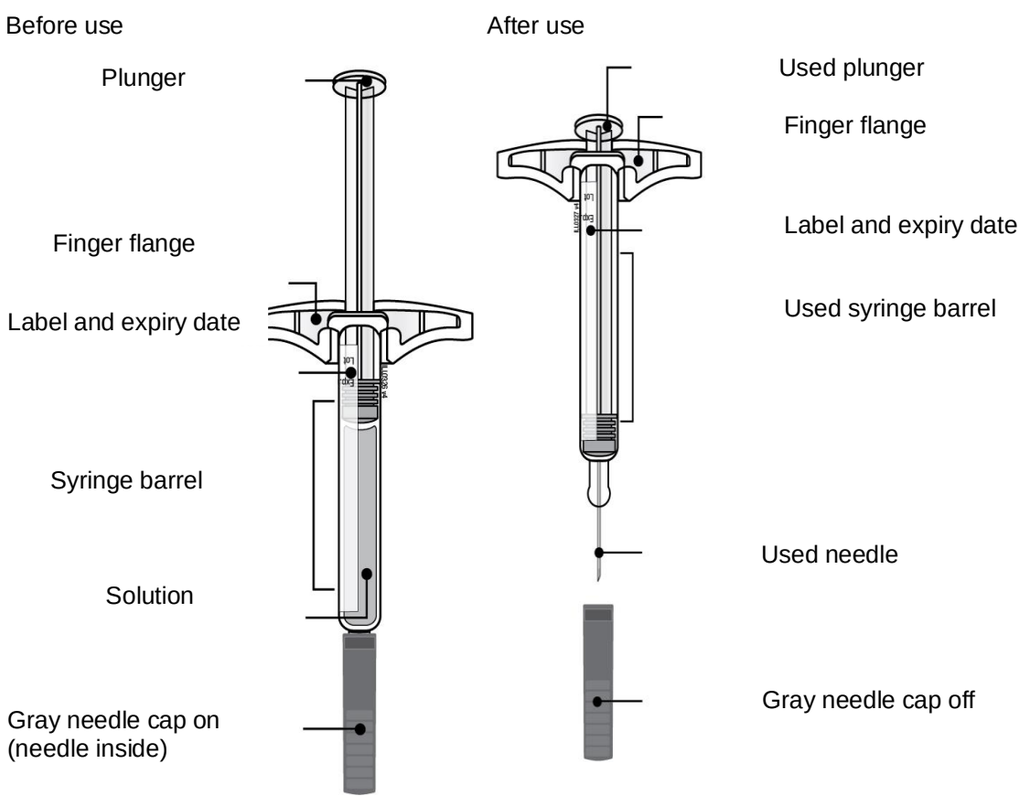
AIMOVIG is provided as:

- Carton of one or two 70 mg/mL or one 140 mg/mL (injection) prefilled syringe with Type 1 glass syringe and stainless steel needle.
- Carton of one or two 70 mg/mL or one 140 mg/mL (injection) prefilled SureClick® autoinjector with Type 1 glass syringe and stainless steel needle.

6.6 Instructions for Use and Handling

Instruction for use of the 70 mg/mL and 140 mg/mL Solution for injection in a Single-Use prefilled Syringe

Single-Use Prefilled Syringe



Important: Needle is inside the grey needle cap

Important

Before you use an AIMOVIG prefilled syringe, read this important information:

Storing your AIMOVIG prefilled syringe

Keep the syringe out of the sight and reach of children.

Keep the syringe in the original carton to protect from light or physical damage.

The syringe should be kept in the refrigerator at 2˚C to 8˚C.

Throw away AIMOVIG that has been left at room temperature (up to 25°C) for more than 7 days.

Do not store the syringe in extreme heat or cold. For example, avoid storing in your car.

Do not freeze.

Using your AIMOVIG prefilled syringe

Do not try to inject AIMOVIG before receiving training from the doctor or nurse.

Do not use a syringe after the expiry date stated on the label.

Do not shake the syringe.

Do not remove the gray needle cap from the syringe until you are ready to inject.

Do not freeze or use the syringe if it has been frozen.

Do not use a syringe if it has been dropped on a hard surface. Part of the syringe may be broken even if you cannot see the break. Use a new syringe, and contact your healthcare provider (doctor, nurse or pharmacist).

This product contains natural rubber latex within the gray needle cap. The product may cause allergic responses in individuals who are sensitized to latex. Tell your healthcare provider if you are allergic to latex.

For more information or help contact your health care provider.

Step 1: Prepare

Read this before you inject.

Check your prescription.

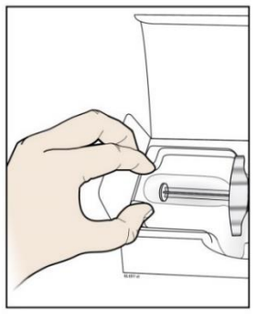
Your healthcare provider has prescribed a 70 mg dose or a 140 mg dose.

For a 70 mg dose, inject one syringe of 70 mg/mL.

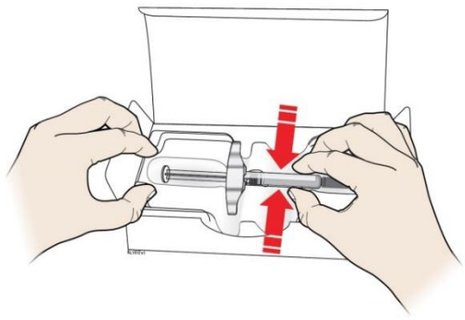
For a 140 mg dose, inject either two syringes of 70 mg/mL, one after the other, or one syringe of 140mg/ml if you were prescribed the 140 mg/mL formulation.

To avoid discomfort at the site of injection, leave the syringe(s) at room temperature for at least 30 minutes before injecting.

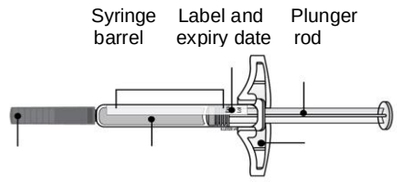
A) Remove the AIMOVIG prefilled syringe(s) from the carton.
Grab the syringe barrel to remove the syringe(s) from the tray.



Place your finger and thumb on the edge of the tray to secure it while you remove the syringe(s).



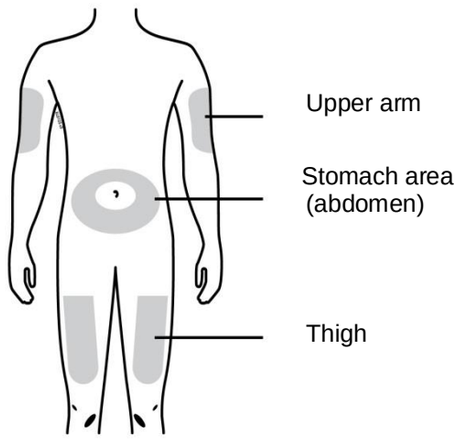
Hold the syringe(s) at the barrel (see arrows).



B) Inspect the AIMOVIG prefilled syringe(s).
Always hold the syringe(s) by the syringe barrel.
Make sure the medicine in the syringe(s) is clear and colorless to slightly yellow.
Leave the syringe(s) at room temperature for at least 30 minutes before injecting.
Do not use the syringe(s) if the medicine is cloudy or discolored or contains flakes or particles.
Do not use the syringe(s) if any part appears cracked or broken.
Do not use the syringe(s) if the syringe has been dropped.
Do not use the syringe(s) if the gray needle cap is missing or not securely attached.
Do not use the syringe(s) if the expiry date printed on the label has passed.
In all cases, use a new syringe, and in case of doubts contact your health care provider.

C) Gather all materials needed for the injections.
Wash your hands thoroughly with soap and water.
On a clean, well-lit work surface, place the:

- One or two new syringes (depending on your prescribed dose)
- Alcohol wipe(s)
- Cotton ball(s) or gauze pad(s)
- Adhesive bandage(s)
- Sharps disposal container



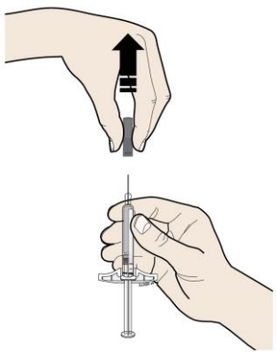
D) Prepare and clean the injection site(s).
Only use these injection sites:

- The thigh
- Stomach area (abdomen), except for a **five** cm area right around the navel
- Outer area of upper arm (only if someone else is giving you the injection)

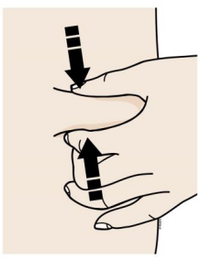
Clean your injection site with an alcohol wipe. Let your skin dry.

- **Do not** touch this area again before injecting.
- Choose a different site each time you give yourself an injection if you need to use the same injection site, make sure it is not the same spot on the injection site you used for a previous injection.
- **Do not** inject into areas where the skin is tender, bruised, red, or hard. Avoid injecting directly into a raised, thick, red, or scaly skin patch or lesion, or areas with scars or stretch marks.

Step 2: Get ready

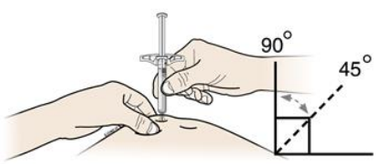


E) Pull the gray needle cap straight out and away from your body, only when you are ready to inject. **Do not** leave the gray needle cap off for more than five minutes. This can dry out the medicine.
It is normal to see a drop of liquid at the end of the needle.
Do not twist or bend the gray needle cap.
Do not put the gray needle cap back onto the syringe.
Do not remove the gray needle cap from the syringe until you are ready to inject.

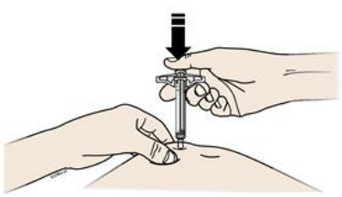


F) Pinch the injection site to create a firm surface.
Pinch skin firmly between your thumb and fingers, creating an area about **five** cm wide.
Important: Keep skin pinched while injecting.

Step 3: Inject



G) While pinching, with the gray needle cap off, insert the syringe into the skin at an angle of 45 to 90 degrees.
Do not place your finger on the plunger rod while inserting the needle.



H) Using slow and constant pressure, push the plunger rod all the way down until it stops moving.

I) When done, release your thumb, and gently lift the syringe off of the skin.

Important: When you remove the syringe, if it looks like the solution is still in the syringe barrel, this means you have not received a full dose. Call your healthcare provider immediately.

Step 4: Finish

J) Discard the used syringe and the gray needle cap.
Put the used AIMOVIG syringe in a sharps disposal container right away after use**. Do not** throw away (dispose of) the syringe in your household trash.
Talk with your healthcare provider about proper disposal. There may be local regulations for disposal.
Do not reuse the syringe.
Do not recycle the syringe or sharps disposal container or throw them into household trash.

Important: Always keep the sharps disposal container out of the sight and reach of children.

K) Examine the injection site.

If there is blood, press a cotton ball or gauze pad on your injection site. **Do not** rub the injection site. Apply an adhesive bandage if needed.

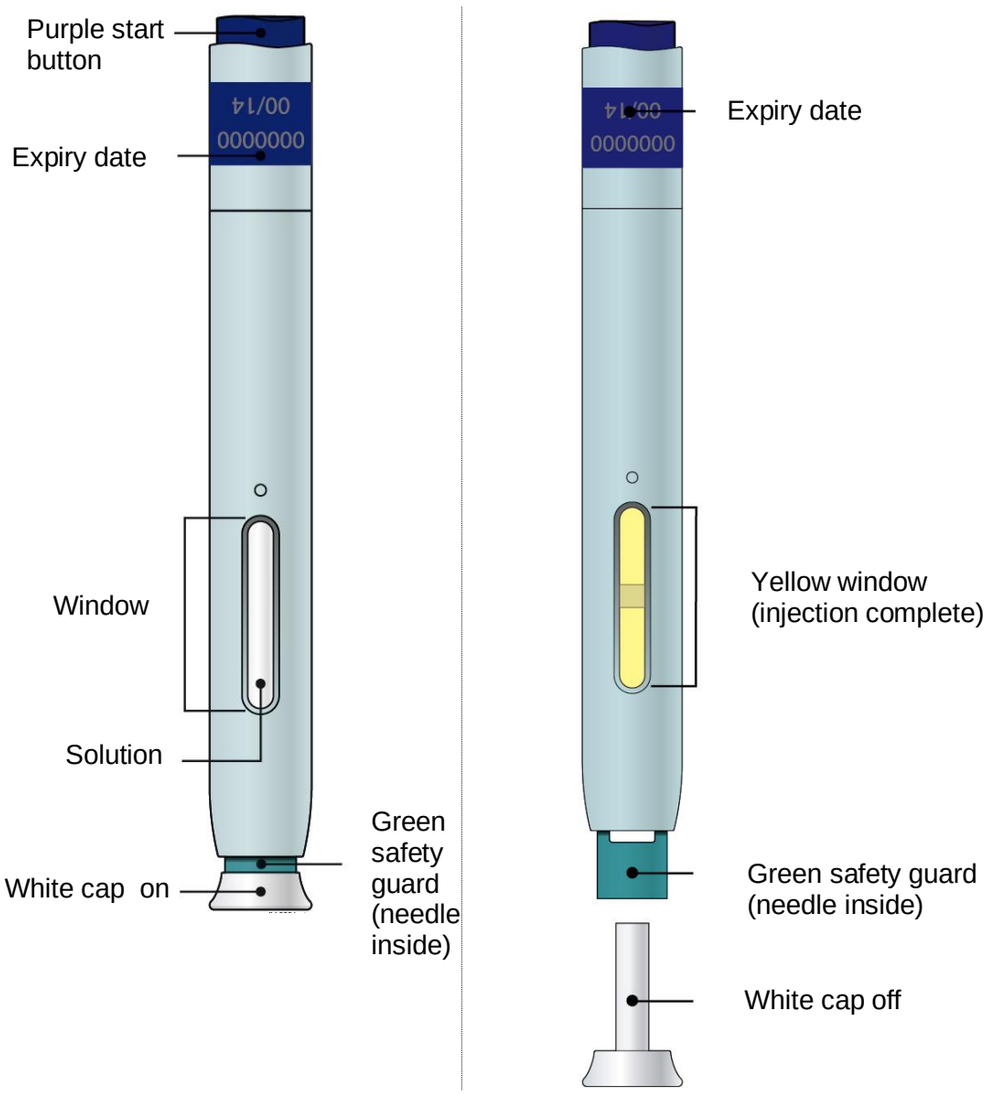
If you were prescribed the 140 mg dose using two 70 mg/mL syringes, repeat steps 1D to 4 with the second syringe to inject your full dose.

Instruction for use of the 70 mg/mL and 140 mg/mL Solution for injection in a Prefilled Single-Use Autoinjector/Pen

Single-Use Autoinjector/Pen 70 mg/mL

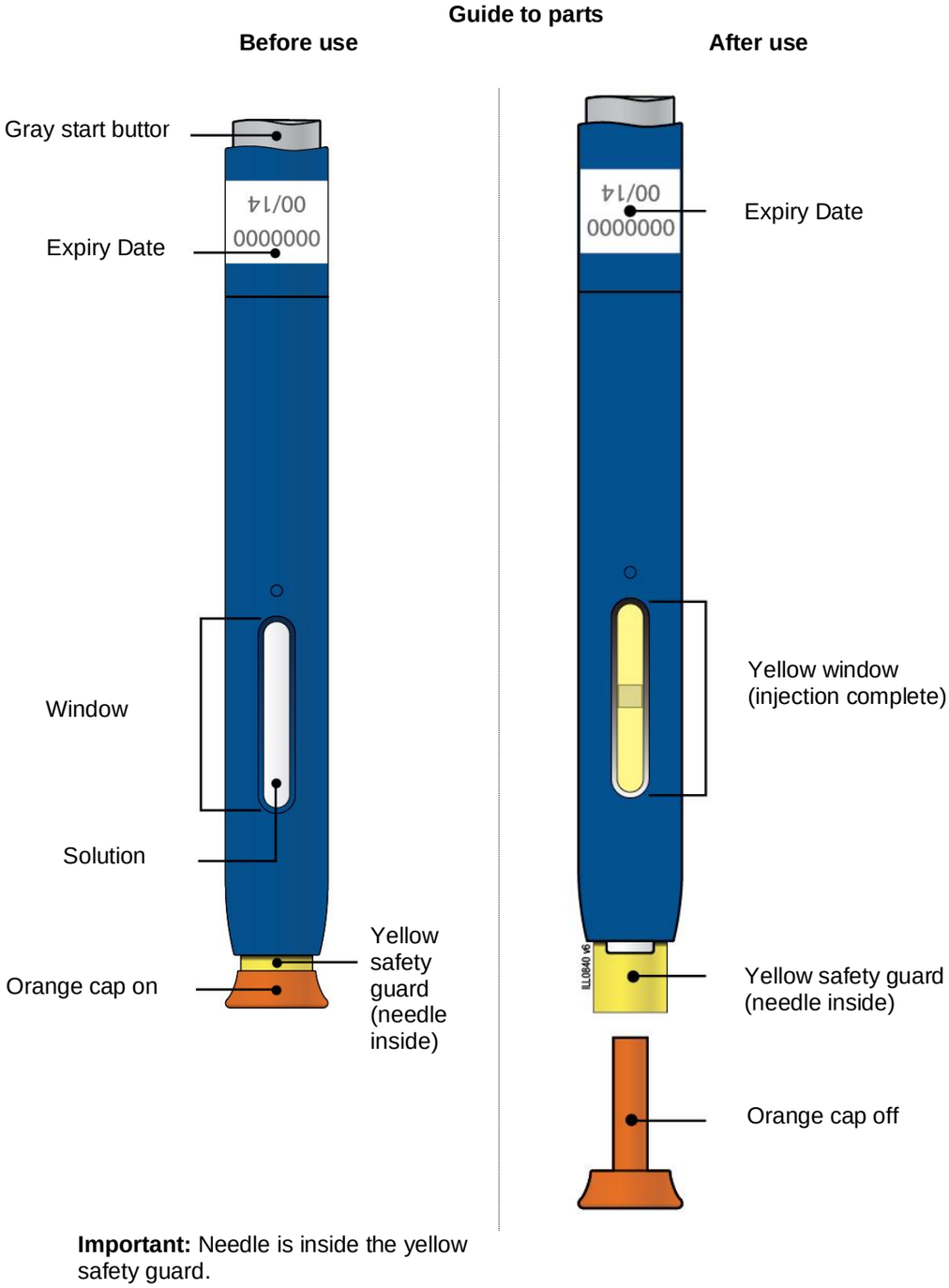
Guide to parts

Before use **After use**



Important: Needle is inside the green safety guard.

Guide to parts



Important: Needle is inside the yellow safety guard.

Important

Before you use an AIMOVIG Single-Use autoinjector, read this important information:

Storing your AIMOVIG autoinjector

- Keep the autoinjector out of the sight and reach of children.
- Keep the autoinjector in the original carton to protect from light or physical damage.
- The autoinjector should be kept in the refrigerator at 2°C to 8°C (36°F to 46°F).
- Throw away autoinjector that has been left at room temperature at 20°C to 25°C (68°F to 77°F) for more than 7 days.
- **Do not** store the autoinjector in extreme heat or cold. For example, avoid storing in your car.
- **Do not** freeze.

Using your AIMOVIG autoinjector

- **Do not try to inject AIMOVIG before receiving training from the doctor or nurse.**
- **Do not** use the autoinjector after the expiration date on the label.
- **Do not** shake the autoinjector.
- **Do not** remove the white or orange cap from the autoinjector until you are ready to inject.

- **Do not** freeze or use the autoinjector if it has been frozen.
- **Do not** use the autoinjector if it has been dropped on a hard surface. Part of the autoinjector may be broken even if you cannot see the break. Use a new autoinjector, and call your healthcare provider (doctor, nurse or pharmacist).

This product contains natural rubber latex within the white or orange cap. The product may cause allergic responses in individuals who are sensitized to latex. Tell your healthcare provider if you are allergic to latex.

For more information or help contact your health care provider.

Step 1: Prepare

Read this before you inject.

Check your prescription.

Your healthcare provider has prescribed a 70 mg dose or a 140 mg dose.

For a 70 mg dose, inject one autoinjector of 70 mg/mL.For a 140 mg dose, inject two autoinjectors of 70 mg/mL, one after the other, or one autoinjector of 140 mg/mL if you were prescribed the 140 mg/mL formulation.

To avoid discomfort at the site of injection, leave the autoinjector(s) at room temperature for at least 30 minutes before injecting.

A) Remove the autoinjector(s) from the carton

Carefully lift the autoinjector(s) straight up out of the carton.

Leave the autoinjector(s) at room temperature for at least 30 minutes before injecting.

Do not put the autoinjector(s) back in the refrigerator once they have reached room temperature.

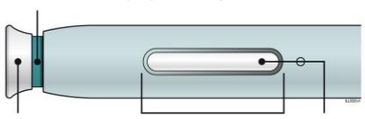
Do not try to warm the autoinjector(s) by using a heat source such as hot water or microwave.

Do not leave the autoinjector(s) in direct sunlight.

Do not shake the autoinjector(s).

Do not remove the white or orange cap from the autoinjector(s) yet.

Green safety guard (needle inside)



White cap on Window Solution

Yellow safety guard (needle inside)

Orange cap on Window Solution

B) Inspect the autoinjector(s)

Make sure the medicine in the window is clear and colorless to slightly yellow

Do not use the autoinjector(s) if the medicine is cloudy or discolored or contains flakes or particles.

Do not use the autoinjector(s) if any part appears cracked or broken.

Do not use the autoinjector(s) if the autoinjector has been dropped.

Do not use the autoinjector(s) if the white cap is missing or not securely attached.

Do not use the autoinjector(s) if the expiration date printed on the label has passed.

In all cases, use a new autoinjector, and in case of doubts contact your health care provider.

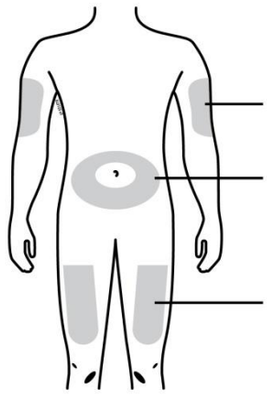
OR

C) Gather all materials needed for your injection(s).

Wash your hands thoroughly with soap and water.

On a clean, well-lit work surface, place the:

- One or two new autoinjector(s)
- Alcohol wipe(s)
- Cotton ball(s) or gauze pad(s)
- Adhesive bandage(s)
- Sharps disposal container



D) Prepare and clean the injection site.

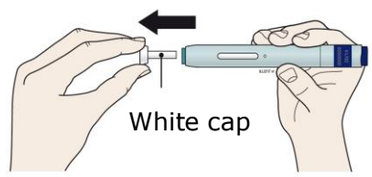
Only use these injection sites:

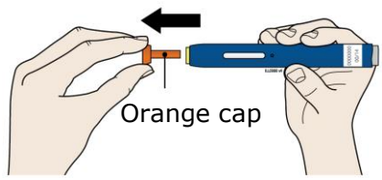
- The thigh
- Stomach area (abdomen), except for a **five** cm area right around the navel
- Outer area of upper arm (only if someone else is giving you the injection)

Clean the injection site with an alcohol wipe. Let the skin dry.

- **Do not** touch this area again before injecting.
- Choose a different site each time you give yourself an injection. If you need to use the same injection site, make sure it is not the same spot on the injection site that you used for a previous injection.
- **Do not** inject into areas where the skin is tender, bruised, red, or hard.
- Avoid injecting directly into a raised, thick, red, or scaly skin patch or lesion, or areas with scars or stretch marks.

Step 2: Get ready





E) Pull the white or orange cap straight off, only when you are ready to inject. **Do not** leave the white or orange cap off for more than five minutes. This can dry out the medicine.

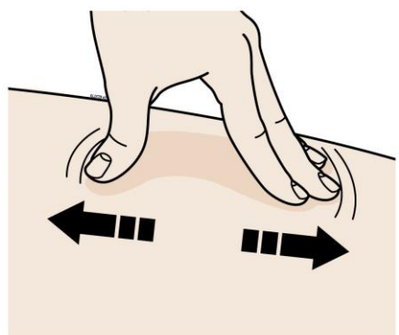
It is normal to see a drop of liquid at the end of the needle or green or yellow safety guard.

Do not twist or bend the white or orange cap.

Do not put the white or orange cap back onto the autoinjector.

Do not put your fingers into the green or yellow safety guard

Do not remove the white or orange cap from the autoinjector until you are ready to inject.



F) Create a firm surface at the selected injection site (thigh, stomach, or outer areas of the upper arm), by using **either** the Stretch method **or** the Pinch method.

Stretch method

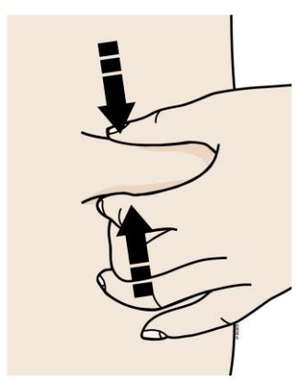
Stretch the skin firmly by moving your thumb and fingers in opposite directions, creating an area about **five** cm wide.

OR

or

Pinch method

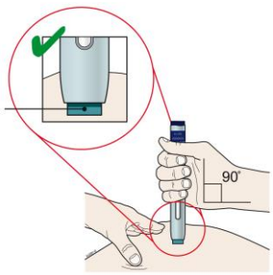
Pinch the skin firmly between your thumb and fingers, creating an area about **five** cm wide.

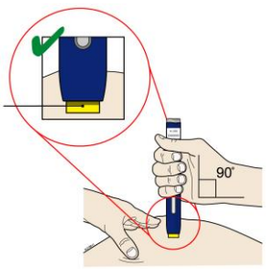


Important: Keep skin stretched or pinched while injecting.

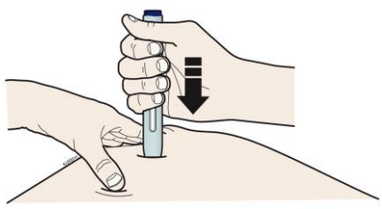
Step 3: Inject

Yellow or Green
safety guard
(needle inside)



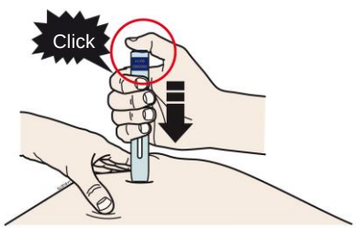


G) Keep holding the stretched or pinched skin. With the white or orange cap off, **put** green or yellow safety guard on the skin at an angle of 90 degrees. The needle is inside the green or yellow safety guard.
Important: Do not touch the purple or gray start button yet.

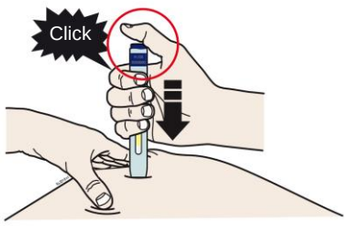


H) Firmly **push** the autoinjector down onto the skin until it stops moving.

Important: You must push all the way down but do not touch the purple or gray start button until you are ready to inject.

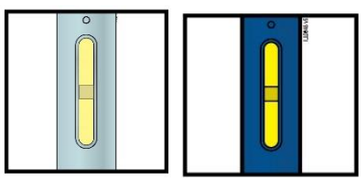


I) When you are ready to inject, **press** the purple or gray start button. You will hear a click.

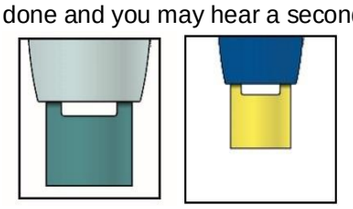


J) Remove your thumb from the button, but keep **pushing** down on the skin. Your injection could take about 15 seconds.

15 seconds



Important Window turns from clear to yellow when injection is done and you may hear a second click.



Note: After you remove the autoinjector from the skin, the needle will be automatically covered.

Important: When you remove the autoinjector, if the window has not turned yellow, or if it looks like the medicine is still being released, this means you have not received a full dose. Contact your healthcare provider immediately.

Step 4: Finish

K) Discard the used autoinjector and the white or orange cap.

Put the used autoinjector in a sharps disposal container right away after use.

Talk with your healthcare provider about proper disposal. There may be local regulations for disposal.

Do not reuse the autoinjector.

Do not recycle the autoinjector or sharps disposal container or throw them into household trash.

Important: Always keep the sharps disposal container out of the sight and reach of children.

L) Examine the injection site.

If there is blood, press a cotton ball or gauze pad on the injection site. **Do not** rub the injection site. Apply an adhesive bandage if needed.

If you were prescribed the 140 mg dose using two 70 mg/mL autoinjectors, repeat steps 1D to 4 with the second autoinjector to inject the full dose.

Commonly asked questions

What will happen if I press the purple or gray start button before I am ready to do the injection on my skin?

Even when you press the purple or gray start button, the injection will only happen when the green or yellow safety guard is also pushed into the autoinjector.

Can I move the autoinjector around on my skin while I am choosing an injection site?

It is okay to move the autoinjector around on the injection site as long as you **do not** press the purple or gray start button. However, if you press the purple or gray start button and the green or yellow safety guard is pushed into the autoinjector, the injection will begin.

Can I release the purple or gray start button after I start my injection?

You can release the purple or gray start button, but continue to hold the autoinjector firmly against your skin during the injection.

Will the purple or gray start button pop up after I release my thumb?

The purple or gray start button may not pop up after you release your thumb if you held your thumb down during the injection. This is okay.

What do I do if I didn't hear a click after pushing the device down on my skin for 15 seconds?

If you didn't hear a click, you can confirm a complete injection by checking that the window has turned yellow.

Whom do I contact if I need help with the autoinjector or my injection?

If you have any questions about the autoinjector, its storage, or about your injection, contact your health care provider.

6.7 Manufacturer

See folding box.

Novartis Pharma AG, Basel, Switzerland